Remarks

Claims 1, 4-6, 9, 10, 12, 13, 18-20 and 25 are pending. No new matter is added herein. Reconsideration of the subject application is respectfully requested.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 1, 4-6, 9, 10, 12, 13, 18-20 and 25 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Klinman et al. (U.S. Patent No. 6,977,245), Cho et al. (Nature Biotechnology, 2000), Alvar et al., (Clinical Microbiology Reviews, 1997) de la Rosa et al., (J. of Clinical Microbiology, 2002) and Chu (U.S. Patent No. 5,175,256). Applicants respectfully disagree with this rejection.

I. Klinman et al. is not available as prior art.

Applicants submit that Klinman *et al.* is not available as prior art under 35 U.S.C. §102(b). As stated in MPEP §2133.02, "Any invention described in a printed publication more than one year prior to the date of a patent application is prior art under Section 102(b), even if the printed publication was authored by the patent applicant. *De Graffenried v. United States*, 16 USPQ2d 1321, 1330 n.7 (Cl. Ct. 1990)". Klinman *et al.* was published on December 20, 2005, which was after the priority date of the subject Application. Thus, Klinman *et al.* is not prior art under 35 U.S.C. §102(b).

U.S. Published Patent Application No. 2003/0060440A1 is the first U.S. patent publication corresponding to Klinman et al. U.S. Published Patent Application No. 2003/0060440A1 was published on March 27, 2003, which is also after the filing date of the present application. U.S. Published Patent Application No. 2003/0060440A1 is not prior art under 35 U.S.C. §102(b).

Thus, Klinman et al. is only available as a reference under 35 U.S.C. § 102(e). M.P.E.P. § 2136.05 set forth that "a 35 U.S.C. 102(e) rejection can be overcome by antedating the filing date (see MPEP § 2136.03 regarding critical reference date of 35 U.S.C. 102(e) prior art) of the reference by submitting an affidavit or declaration under 37 CFR 1.131 or by submitting an affidavit or declaration under 37 CFR 1.132 establishing that the relevant disclosure is applicant's own work. *In re Mathews*, 408 F.2d 1393, 161 USPQ 276 (CCPA 1969)."

Submitted herewith is a Declaration under 37 C.F.R. §1.132 by Dennis M. Klinman and Daniela Verthelyi, the inventors of the subject application. As indicated in the Declaration, any subject matter of the claimed invention that is described in Klinman *et al.* is the work of the inventors alone. The other co-inventors of Klinman et al., namely, Ken Ishii, James J. Mond and Mayda Gursel, contributed to the oligodeoxynucleotides (ODNs) claimed in Klinman et al., but did not contribute to methods for treating *Leishmania* using a nucleic acid comprising SEQ ID NO: 176, SEQ ID NO: 177 and/or SEQ ID NO: 178. Thus, under the guidelines stated in MPEP §2132.01, the Declaration demonstrates that Klinman *et al.* merely describes the inventors' own work and not that "by another."

Thus, it is established that Klinman *et al.* is not prior art under 35 U.S.C. §102(b), and that all the relevant disclosure in Klinman et al. is the inventors' own work.

II. The remaining references do not disclose all of the elements of the claimed methods

Cho *et al.* describe vaccination of healthy animals with an immunostimulatory DNA sequence (TGACTGTGAACCTTCGAGAT) that includes the immunostimulatory motif 5' Pu-Pu-CpG-Py-Py-3' (ISS) conjugated to ovalbumin and evaluating CTL activity and cytokine production in response to the vaccine. Animals receiving the vaccine were protected against a lethal burden of OVA-expressing tumor cells.

Cho *et al.* merely postulate that a vaccine comprising an ISS-DNA sequence could be used to induce protective immunity, such as to produce an immune response to HIV itself (see page 513). However, there is no teaching or suggestion in Cho et al. that ISS DNAs could be used to produce an immune response to a secondary infection. In fact, there is no mention or suggestion in Cho et al. of the production of an immune response to any secondary infection, let alone *Leishmania.*

Cho et al. only disclose that ISS-DNA can be used to induce an immune response to ovalbumin. Cho et al. does not demonstrate the induction of an immune response in immunocompromised animals, let alone subjects infected with an immunodeficiency virus.

In addition, a D-type ODN has a very different formula (5' $X_1X_2X_3$ Pu_1 Py_2 CpG Pu_3 Py_4 $X_4X_5X_6(W)_M(G)_N$-3') than the ODNs dislcosed by Cho et al. (5' Pu-Pu-CpG-Py-Py-3'). None

of the experiments performed by Cho *et al.* utilize a D-type ODN, nor can they been construed to suggest the use of a D-type ODN. Furthermore, Cho et al. do not disclose or suggest the use of the nucleic acid sequences set forth as SEQ ID NO: 176, SEQ ID NO: 177 and/or SEQ ID NO: 178.

Alvar *et al.* discloses that there is often co-infection with *Leishmania* and human immunodeficiency virus. Alva *et al.* disclose that the drug choice for treatment of Leishmania in HIV positive patients are antimonial salts, amphotericin B, or a combination of antimonial compounds with allopurinol, aminosidine or interferon (IFN)-γ (see page 310-311). Alvar *et al.* discloses that additional treatments, such as petamindine, azoles, and itraconaxole have been tried, but there is no data that supports the usefulness of these drugs (see page 311). Alvar *et al.* does not disclose the use of any ODN-based therapy, such as an immunostimulatory ODN, for the treatment of *Leishmania* in an immunocompromised subject. Thus, Alvar *et al.* do not make up for the deficiencies of Cho *et al.*

De la Rosa *et al.* disclose that the use of highly active antiretroviral therapy (HAART) leads to a fall in the incidence of symptomatic visceral leishmaniasis in a subject infected with HIV-1. Deep immunosuppression was the main risk factor associated with kala-azar emergence in subject infected with HIV. However, de la Rosa *et al.* does not disclose the use of any ODN-based therapy, such as an immunostimulatory ODN, for the treatment of *Leishmania* in an immunocompromized subject. Thus, de la Rosa *et al.* do not make up for the deficiencies of Cho *et al.* and/or Alvar *et al.*

Chu (U.S. Patent No. 5,175,267) is a patent entitled "Stereoselective Glycosylation of Heterocyclic Basis." Chu discloses that the synthetic nucleoside 3'-azido-3'-deoxythymidine (AZT) inhibits the replication of HIV-1 and HIV-2. However, Chu does not disclose the use of any ODN-based therapy, such as an immunostimulatory ODN, for any treatment, let alone the treatment of *Leishmania* in an immunocompromised subject. Thus, Chu does not make up for the deficiencies of Cho *et al.* and/or Alvar *et al.* and/or de la Rosa *et al.*

Thus, the prior art, alone or in combination, does not teach all of the elements of the presently claimed methods. Applicants submit that there is no *prima facie* case of obviousness.

III. Evidence of an unexpectedly superior result overcomes any prima facie case of obviousness.

Even if the Office were to maintain that the pending claims are *prima facie* obvious in view of the cited prior art (which the Applicants believe is not correct), the Applicants submit that the claimed methods provide unexpectedly superior results, as discussed in the prior Declaration under 37 C.F.R. § 1.132 (submitted with the response filed on June 5, 2008, hereinafter "the prior Declaration"), the response filed January 2, 2009, the response filed July 17, 2009, the response filed January 4, 2010, and the response filed July 13, 2010. The most pertinent aspects of the prior responses are provided below for the Examiner's convenience.

Pages 4-5 of the prior Declaration describe the results obtained when a combination of D ODNs (D19 – SEQ ID NO: 176; D35 – SEQ ID NO: 177; and D29 – SEQ ID NO; 178) were evaluated in an art-accepted macaque model of HIV. Macaques that had been infected for greater than 12 months with SIV Mac239, and had viral loads ranging from 0.3-28 x 10^6 copies/ml, were used in these studies. The animals were stratified based on viral load and then challenged with *L. major* metacyclic promastigotes (MHOM/IL/80/Friedlin). Healthy macaques challenged with *L. major* developed cutaneous lesions characterized by erythema, induration and ulceration that peaked 25 days after challenge and resolved within 50 days (see Fig. 3A of the Declaration). Due to their immunosuppressed state, untreated macaques developed severe progressive cutaneous lesions that did not resolve. The severity of *Leishmania* infection in SIV-infected animals treated with K ODN (another type of immunostimulatory ODN) was not significantly different from that of the controls.

In contrast, SIV-infected macaques treated with the combination of D ODN as recited in pending claims 1 and 25, developed significantly smaller lesions, and their infection did not progress over time (Fig. 3A of the Declaration) as compared to controls. The animals were euthanized on day 56, and their parasite burden measured. SIV-infected monkeys treated with D ODN had a 35-fold reduction in total parasite burden at the lesion site compared to SIV-infected animals treated with control ODN or saline (see Fig. 3B of the Declaration, $p<0.001$). The

comparative data, both with regard to the type of ODN used (D versus K), and the type of immune response achieved (general response versus a response to a secondary infection) demonstrate the unexpectedly superior result that is achieved using the claimed methods.

Verthelyi *et al.* (*J. Immunol.* 170: 4717-4723, 2003; of record) provides additional evidence of the superior results achieved with the claimed methods. This post-filing date publication provides additional evidence that the specific combination of D ODNs recited in the pending claims can be used to induce an immune response to *Leishmania* in macaques infected with an immunodeficiency virus (SIV). Macaques treated with the D ODNs developed significantly smaller lesions, and their infection did not progress over time. However, the severity of *Leishmania* infection in animals treated with immunostimulatory K ODNs was not significantly different than controls. Monkeys treated with the claimed combination of D ODNs had a 35-fold reduction in parasite burden at the lesion site. This provides additional evidence of the unexpectedly superior results achieved using the claimed methods.

The demonstration of an unexpectedly superior result overcomes any *prima facie* case of obviousness that could be made based on the prior cited art.

Reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

It is respectfully requested that the amended claims submitted herewith should all be recombined and considered in the current case. The Examiner is formally requested to contact the undersigned prior to issuance of the next Office action, in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

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